Femoral Adipose Tissue May Accumulate the Fat That Has Been Recycled as VLDL and Nonesterified Fatty Acids

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OBJECTIVE—Gluteo-femoral, in contrast to abdominal, fat accumulation appears protective against diabetes and cardiovascular disease. Our objective was to test the hypothesis that this reflects differences in the ability of the two depots to sequester fatty acids, with gluteo-femoral fat acting as a longer-term "sink."

RESEARCH DESIGN AND METHODS—A total of 12 healthy volunteers were studied after an overnight fast and after ingestion of a mixed meal. Blood samples were taken from veins draining subcutaneous femoral and abdominal fat and compared with arterialized blood samples. Stable isotope-labeled fatty acids were used to trace specific lipid fractions. In 36 subjects, adipose tissue blood flow in the two depots was monitored with ^{133}Xe.

RESULTS—Blood flow increased in response to the meal in both depots, and these responses were correlated ($r_s = 0.44$, $P < 0.01$). Nonesterified fatty acid (NEFA) release was suppressed after the meal in both depots; it was lower in femoral fat than in abdominal fat ($P < 0.01$). Plasma triacylglycerol (TG) extraction by femoral fat was also lower than that by abdominal fat ($P = 0.05$). Isotopic tracers showed that the difference was in chylomicron-TG extraction. VLDL-TG extraction and direct NEFA uptake were similar in the two depots.

CONCLUSIONS—Femoral fat shows lower metabolic fluxes than subcutaneous abdominal fat, but differs in its relative preference for extracting fatty acids directly from the plasma NEFA and VLDL-TG pools compared with chylomicron-TG. ***Diabetes*** **59:2465–2473, 2010**

Obesity is associated with increased risk of coronary heart disease and type 2 diabetes. The distribution of body fat is an important factor in this relationship. The ratio of abdominal to lower-body (gluteo-femoral) fat accumulation, measured by the waist-to-hip ratio, is a major determinant of adverse metabolic consequences and mortality, independent of the degree of obesity (1,2). In recent years, it has become clear that not only is lower-body fat less harmful than abdominal fat, but it actually provides protection against coronary heart disease and type 2 diabetes (rev. in 3).

The reason for the different relationships of these two major fat depots to metabolic health is not clear. On the basis of in vitro observations, it has been postulated that lipolysis, and hence delivery of nonesterified fatty acids (NEFAs) into the systemic circulation, is greater in abdominal adipose tissue (4,5) and less readily suppressed by insulin (6). These arguments have been extended to visceral fat, which has a high rate of lipolysis in vitro (7,8), and in many studies is the depot most closely associated with metabolic risk (9,10). However, it is evident that this explanation alone cannot be sufficient, since any fat depot with a high rate of lipolysis should disappear unless fat mobilization is matched by a high rate of fatty acid uptake, i.e., a high rate of turnover (11).

The most consistent argument for the protective properties of lower-body fat, viewed in that light, is that lower-body fat depots provide a long-term energy store and hence act as a "metabolic sink" for excess fat, protecting other tissues from excessive exposure to fatty acids (12; rev. in 3). In support of this hypothesis is the fact that the gluteo-femoral depots are lost more slowly than abdominal depots during an energy deficit (13–15). Direct measurements of fat turnover after oral administration of radio-labeled fat show faster turnover in subcutaneous abdominal than femoral fat (16). Several studies have been made of the short-term adipose tissue uptake of radio-labeled dietary fat. In lean people, short-term uptake of meal-derived fatty acids is greater in subcutaneous abdominal than in femoral adipose tissue, because of greater efficiency of uptake and greater adipose tissue mass (17,18). However, women with lower-body obesity store more dietary fat over 24 h in the lower body (gluteal fat depot) than women with upper-body obesity or obese men (15). In addition, lean women, as compared with men, preferentially store fat in their lower-body adipose tissue when fed a high-fat high-calorie meal (19).

Little is known of the physiological and metabolic responses at the tissue level that lead to these differences in handling of excess fat. For instance, an increase in adipose tissue blood flow (ATBF) after meal intake (20) may have a role in presenting substrate to lipoprotein lipase (LPL) in adipose tissue capillaries for uptake (21) and delivering signals such as insulin to promote fat storage. Studies of the regulation of ATBF in different depots have given divergent results (reviewed in DISCUSSION). LPL activity measured in biopsies in the fed state is correlated with meal fatty acid uptake and is greater in femoral fat than in abdominal fat (19,22), but physiological measurements of LPL action in vivo, which would include the effects of ATBF, have not been made.

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We hypothesized that the action of gluteo-femoral adipose tissue as a metabolic sink might be most apparent in the fed state and would be reflected in a greater ability of femoral than abdominal adipose tissue to entrap dietary fatty acids. The metabolic physiology of the subcutaneous abdominal fat depot has been investigated extensively using measurements of ATBF in conjunction with arterio-venous difference measurements (23). Recently, we described a similar technique for studying the metabolic physiology of the subcutaneous femoral adipose depot (24). Here we report the first direct comparisons of the physiological and metabolic responses of the two adipose depots to meal ingestion.

RESEARCH DESIGN AND METHODS

Participants and protocol. We studied ATBF responses to meal ingestion in 36 healthy nonobese subjects (18 males and 18 females comparable for age and BMI). In a subgroup of 12 of these volunteers (eight males), we conducted detailed studies of metabolic physiology by measurement of arterio-venous differences across the two depots.

Volunteers were recruited from the greater Oxford community by advertisement or from the Oxford BioBank (25). The protocol was approved by the Oxfordshire Research Ethics Committee, and all participants gave written informed consent. None of the subjects was taking medication known to affect lipid metabolism and all were normoglycemic. They were asked to consume a corn-free diet for 48 h before the study and to refrain from strenuous exercise and alcohol for 24 h before the study. They attended the Oxford Centre for Diabetes, Endocrinology and Metabolism Clinical Research Unit, having fasted from 10:00 P.M. the previous night.

ATBF was measured in subcutaneous abdominal and femoral depots with the ^{133}Xe washout method, as described previously (26), in the fasting state and after the ingestion of a mixed meal. The mixed meal contained 40 g fat as olive oil in the form of a chocolate-flavored emulsion with 400 mg emulsifier and flavorings and 40 g carbohydrate as Rice Krispies (Kellogg, Manchester, U.K.) with skimmed milk (200 g) (27).

In the "metabolic study" subgroup, arterio-venous differences were measured across abdominal and femoral adipose tissue. A superficial epigastric vein draining subcutaneous abdominal fat (28), a branch of the great saphenous vein draining femoral fat (24), and an arterialized dorsal hand vein (with the hand kept in a warming box at 60°C) were cannulated. The cannulae were kept patent with 0.9% saline. We used plasma creatinine concentrations as an indication of contamination by muscle venous blood (24).

Stable isotope-labeled fatty acids were used to trace different lipid pools as described previously (29). A constant infusion of [$^2H_2$]palmitate (CK Gas Products, Hampshire, U.K.) was given intravenously (0.01 μmol $\cdot$ kg^{-1} $\cdot$ min^{-1}) in 400 ml human albumin (4.5%) throughout the study to trace endogenous fatty acid metabolism and the VLDL-triacylglycerol (TG) pool (produced in the liver after hepatic uptake of labeled plasma NEFAs). [U^{13}C]palmitate (100 mg) was added to the fat emulsion as part of the mixed meal (29) to trace exogenous (dietary) fatty acid metabolism.

In the metabolic study subgroup, blood samples were taken simultaneously from all three sites at baseline (−30 and 0 min) and at 30, 60, 90, 120, 180, 240, 300, and 360 min after the meal. Skin temperatures were measured throughout the study at regular intervals. Abdominal and thigh skin temperatures remained relatively constant, and no differences between sites were noted.

Analytical methods. Blood samples were drawn into heparinized syringes (Sarstedt, Leicester, U.K.), and plasma was prepared rapidly at 4°C. Glucose concentrations were measured immediately, and remaining samples were frozen before analysis. Plasma TG, NEFAs, glucose, and creatinine were analyzed enzymatically using commercially available kits on an ILAB600 or ILAB650 clinical analyzer (Instrumentation Laboratory U.K., Warrington, U.K.), and insulin was measured by radioimmunoassay (Millipore, Watford, U.K.).

Chylomicron (S_f <400) and VLDL (S_f 20–400) fractions were prepared from plasma by sequential flotation in the ultracentrifuge as described previously (29). TG concentrations were measured enzymatically as above.

Lipid fractions (NEFA and TG) were separated, and fatty acid composition and tracer enrichment were analyzed by gas chromatography and mass spectrometry as described previously (29). Enrichments were converted to tracer-to-tracee ratios.

Calculations and statistics. ATBF was calculated from the washout of ^{133}Xe assuming a partition coefficient of 10 ml/g for both depots (30). Although this may not be accurate for each individual, the emphasis in this study was on changes induced by feeding within depots and on correlations between the depots. There is no consistent difference in partition coefficient between subcutaneous abdominal and thigh adipose tissue (30,31). Baseline ATBF was taken as the average at time −30 and 0 min. Peak ATBF was calculated as the greatest mean of three adjacent points after the meal (20). The ATBF response to the meal was calculated as peak minus baseline.

Metabolic calculations were made as described previously (29) and are described in RESULTS. We calculated chylomicron- and VLDL-TG extraction across the tissues directly, based on the rates of extraction of [^{13}C]palmitate in TG and [$^2H_2$]palmitate in TG, respectively. They were multiplied by the appropriate tracer-to-tracee ratio and percentage of palmitate in TG. Net transcapillary flux of fatty acids across adipose tissue was calculated as the difference between total arterialized and total venous fatty acids [$(TG \times 3 + NEFA)_{arterial} - (TG \times 3 + NEFA)_{venous}$] (32). It represents the net flux of fatty acids between adipocytes and capillaries. We applied the same calculation to isotopically labeled fatty acids to represent the handling of all fatty acids (TG and NEFA) arising from chylomicron and VLDL fractions.

Data were analyzed using SPSS Statistics, version 17.0. Repeated measures (RM)-ANOVA with time and site as within-subject factors was used to identify time and site effects, and sex was used as a between-subject factor to identify sex effects. Spearman rank correlation coefficient (r_s) was used to test for associations. Data are presented as mean ± SE unless otherwise stated.

TABLE 1
Characteristics of participants in the ATBF study

	Men	Women
n	18	18
Age (years)	34.0 ± 10.8	36.6 ± 13.2
BMI (kg/m^2)	24.4 ± 2.8	23.5 ± 2.7
Body fat (%)	16.6 ± 1.4	28.1 ± 1.4*
Waist-to-hip ratio	0.88 ± 0.08	0.78 ± 0.01

Data are means ± SD or *n*. *$P < 0.001$.

RESULTS

Adipose tissue blood flow. Characteristics of the participants in whom ATBF was studied are given in Table 1. Age and BMI of the male and female participants were similar, but as expected, the females had greater body fat content.

There was no difference in fasting ATBF between subcutaneous abdominal and femoral depots ($P = 0.64$). After the mixed meal, ATBF increased in both depots (Fig. 1*A*), with significant main effects of time ($P < 0.001$) and site ($P = 0.003$) by RM-ANOVA. The peak was on average at 60 min and was higher in the abdominal than the femoral depot ($P = 0.01$). There were no sex differences in fasting or in postprandial abdominal or femoral ATBF (not shown).

In the whole group, there was a positive relationship between fasting and peak ATBF within both abdominal and femoral AT depots ($r_s = 0.67$ and $r_s = 0.64$, respectively, each $P < 0.001$). Comparing the two depots, there was no correlation between fasting ATBF in the abdominal and femoral depots ($r_s = 0.15$, $P = 0.38$). However, peak abdominal and peak femoral ATBF were positively correlated ($r_s = 0.53$, $P < 0.001$), and the blood flow response (peak − baseline) in abdominal adipose tissue was correlated with the blood flow response in femoral adipose tissue ($r_s = 0.44$, $P < 0.01$).

Peak postprandial ATBF and, to a lesser extent, the ATBF response were negatively related to measures of adiposity. These associations were generally weaker for femoral than for abdominal ATBF (e.g., peak ATBF vs. BMI, $r_s = -0.47$, $P < 0.01$; $r_s = -0.36$, $P = 0.03$, for abdominal and femoral fat, respectively). These relationships also existed for waist and hip circumference (versus peak abdominal ATBF, $r_s = -0.44$, $P < 0.01$; $r_s = -0.43$, $P < 0.01$, respectively). There was no consistent pattern of

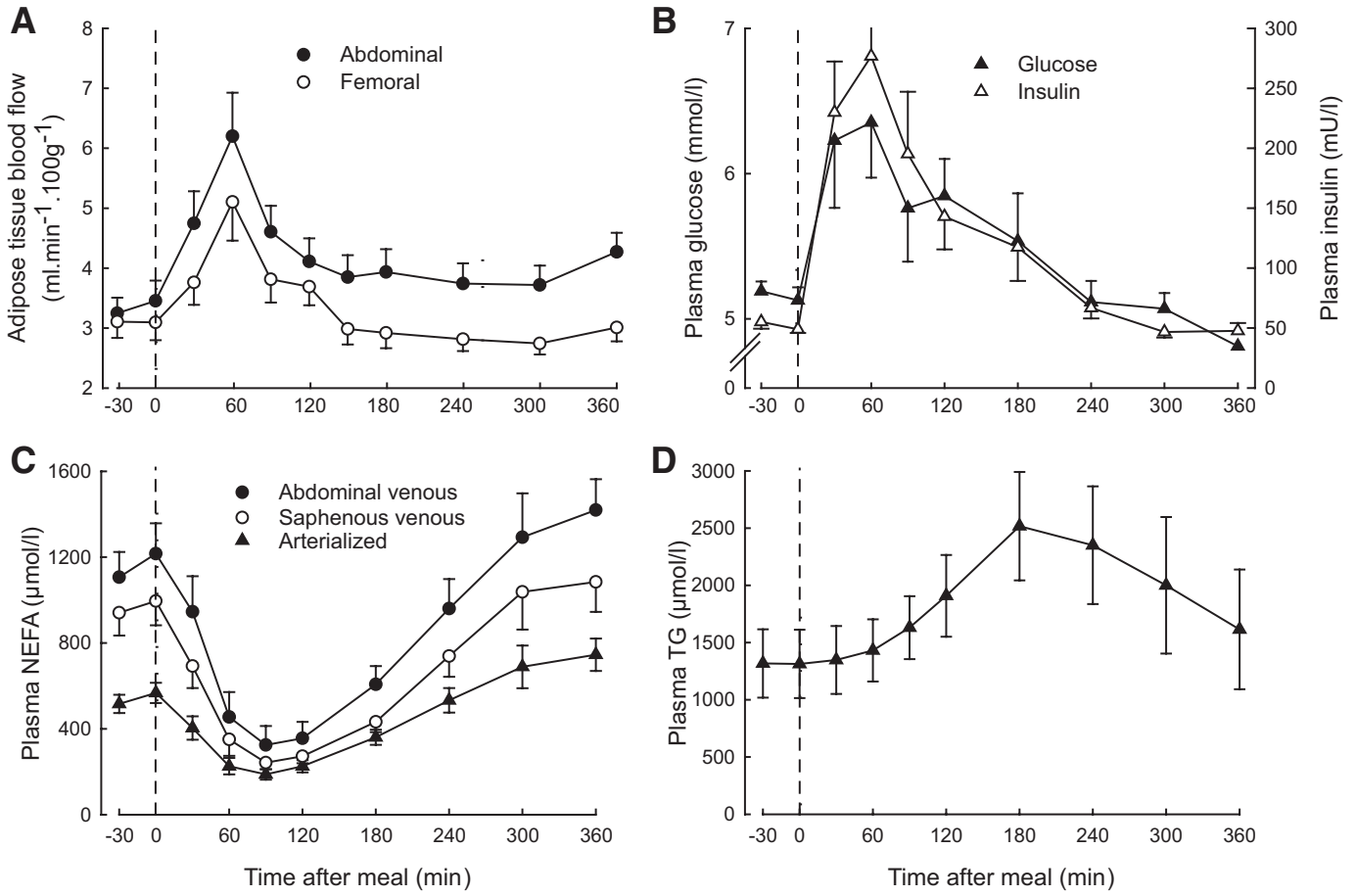


FIG. 1. ATBF and systemic concentrations in the fasting and postprandial states. *A*: ATBF. *n* = 36. *B*: Arterialized plasma glucose and plasma insulin. *C*: Plasma NEFAs. *D*: Arterialized plasma TG. For *B*, *C*, and *D*, *n* = 12.

association with blood flow in either depot and either waist or hip circumference in men compared with women. It should be noted that waist and hip circumferences were themselves positively correlated within each sex (males, $r_s = 0.68$, $P = 0.002$; females, $r_s = 0.57$, $P = 0.01$) and over the whole group ($r_s = 0.59$, $P < 0.001$).

Metabolic study: systemic concentrations. Characteristics of the participants in the metabolic substudy are shown in Table 2.

ATBF in this subgroup followed a similar pattern to that in the larger group (Fig. 1*A*). Systemic concentrations of glucose, insulin, and TG rose after the meal, whereas those of NEFAs fell (Fig. 1*B–D*). There was consistent extraction of glucose and TG across both depots and release of NEFA (raw concentrations are shown in Fig. 1*C*).

Creatinine concentrations were similar in the three sampling sites (Fig. 2*A*), although there was a small but significant site effect. Mean concentrations averaged over the experimental period were as follows: arterial 67.9 ± 3.8 μmol/l, abdominal adipose venous 66.7 ± 3.7 μmol/l, and femoral adipose venous 69.0 ± 3.8 μmol/l. (For comparison, concentrations in a vein draining skeletal muscle are typically 20% greater than in arterial blood [24].)

TABLE 2
Characteristics of participants in the metabolic study

n (M/F)	12 (8/4)
Age (years)	32.3 ± 11.3
BMI (kg/m^2)	24.2 ± 3.1
Body fat (%)	20.4 ± 8.3
Waist-to-hip ratio	0.85 ± 0.07

Data are means ± SD or *n*. These participants were a subset of the 36 participants in the ATBF study.

Adipose tissue substrate fluxes. Glucose uptake was identical in the two depots in the fasting state and increased in both depots after the meal (Fig. 2*B*), with an early peak but otherwise mirroring arterialized glucose concentrations. NEFA release (Fig. 2*C*) tended to be lower in the fasting state in femoral compared with subcutaneous abdominal adipose tissue ($P = 0.1$). It suppressed similarly after the meal in both depots, but was significantly lower in femoral than in abdominal adipose tissue. TG extraction (Fig. 2*D*) was similar in the two depots in the fasted state. It increased in both after the meal, but tended to be lower in the femoral than the subcutaneous abdominal depot.

For each of these parameters, sex effects were investigated by including sex as a between-subjects factor in the RM-ANOVA. For glucose uptake, there was a time × sex interaction ($P = 0.03$) reflecting a greater peak value in the men in both depots. This was not seen for either NEFA release or TG extraction.

Measures of net fatty acid retention in the two adipose tissue depots are shown in Fig. 3. Transcapillary fatty acid flux (Fig. 3*A*), reflecting the net movement of fatty acids in and out of adipocytes (32), was negative (fat mobilization) in the fasting state and became positive (fat storage) after

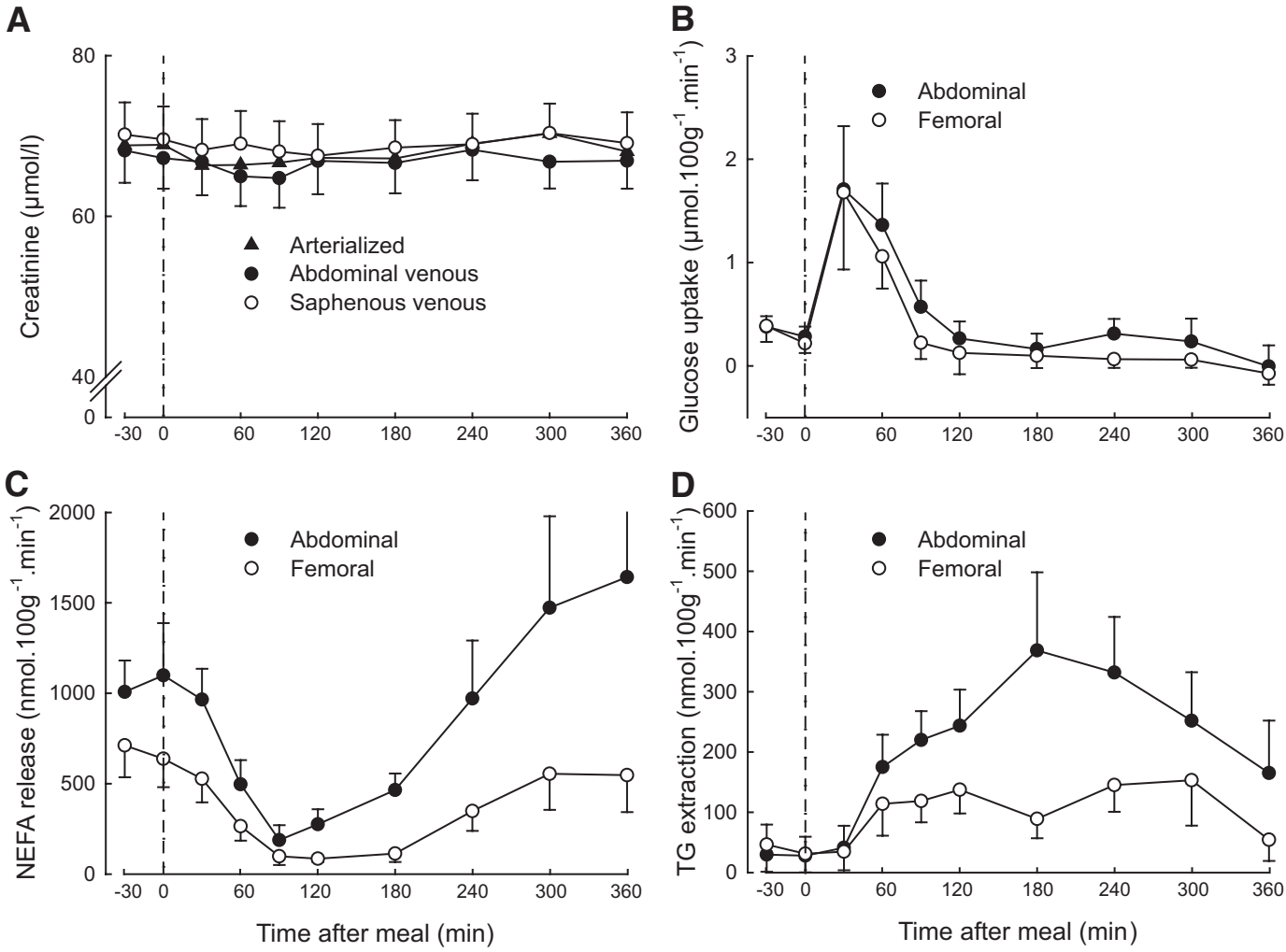


FIG. 2. Tissue-specific responses in the fasting and postprandial states. *A*: Plasma creatinine. *B*: Adipose tissue glucose uptake. *C*: Adipose tissue NEFA release. *D*: Adipose tissue TG extraction. RM-ANOVA shows the following: creatinine, main effects of site ($P = 0.004$) and time ($P = 0.007$); glucose uptake, main effect of time ($P = 0.01$), no effect of site or time × site interaction; NEFA release, main effects of time and of site ($P < 0.01$) with time × site interaction ($P = 0.02$); TG extraction, main effects of time ($P = 0.01$) and site ($P = 0.052$) (interaction, $P = 0.07$).

the meal in both depots. In the fasting state, it tended to be less negative in femoral than in subcutaneous abdominal adipose tissue ($P = 0.06$); after the meal, it responded less, with a significant time × site interaction ($P = 0.02$). Fractional re-esterification of fatty acids within adipose tissue was calculated from the mass balances of NEFA and glycerol (Fig. 3*B*). In the fasting state, it was similar in the two depots and correlated between them ($r_s = 0.60$, $P = 0.04$, Fig. 3*C*). It increased in both depots after the meal and remained higher in the femoral than the subcutaneous abdominal tissue in the late postprandial period. Average values over the postprandial period were also highly correlated between the two depots ($r_s = 0.93$, $P < 0.001$, Fig. 3*D*). Neither sex nor insulin concentrations were involved in these close relationships between the two depots, nor were BMI and percentage body fat.

Whole-depot responses were estimated using depot fat masses measured by dual-energy X-ray absorptiometry in seven volunteers. These data are shown in supplementary Table 1 in the online appendix (available at http://diabetes.diabetesjournals.org/cgi/content/full/db10-0678/DC1) and confirm the greater substrate fluxes in abdominal fat on a whole-depot basis.

Tracer studies. The pathways of fat uptake were further investigated using the tracer fatty acids, [^{13}C]palmitate incorporated into the dietary fat, and [$^{2}H_2$]palmitate, which was infused to label both the plasma NEFA and the newly synthesized VLDL-TG pools.

Both adipose depots extracted [^{13}C]TG-palmitate (representing chylomicron-TG), with a peak rate at 120–180 min and, similar to total plasma TG extraction (Fig. 2*D*), the rate was lower in femoral than in subcutaneous abdominal adipose tissue ($P = 0.02$). Chylomicron-TG extraction calculated based on these data are shown in Fig. 4*A*. It was also lower in femoral than in subcutaneous abdominal adipose tissue. Both adipose depots demonstrated "spillover" of chylomicron-derived fatty acids, assessed by the appearance of ^{13}C-labeled palmitate in the venous plasma (33) (Fig. 4*B*). This was lower in the femoral than the subcutaneous abdominal adipose depot, reflecting lower extraction of ^{13}C-labeled TG as above. Fractional spillover of ^{13}C-labeled fatty acids (i.e., the proportion of those ^{13}C-labeled fatty acids released by LPL that enter the plasma NEFA pool) was therefore not different between the depots ($P = 0.65$).

In contrast, handling of [$^{2}H_2$]palmitate, the infused tracer marking both the plasma NEFA pool and newly synthesized VLDL-TG, was not different between the depots. Directly measured [$^{2}H_2$]TG-palmitate extraction was similar in the two depots, as was VLDL-TG extraction

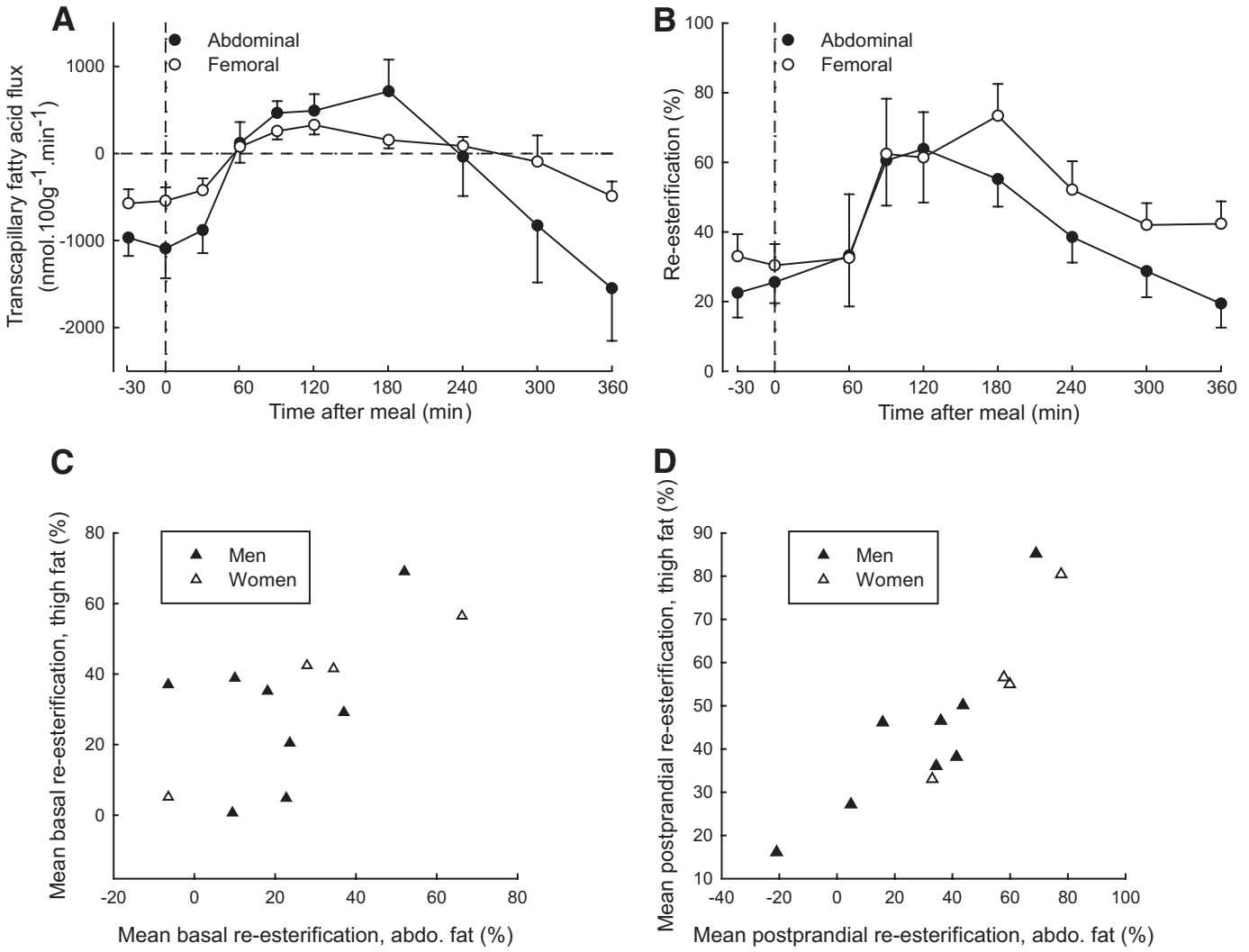


FIG. 3. Measures of net fatty acid retention in adipose tissue in the fasting and postprandial states. *A*: Net transcapillary flux of fatty acids. *B*: Percentage re-esterification of fatty acids. Both *A* and *B* were calculated from mass balances as in RESEARCH DESIGN AND METHODS. RM-ANOVA shows the following: net transcapillary flux, main effect of time ($P = 0.001$) and time × site interaction ($P = 0.019$); percentage re-esterification, main effect of site ($P = 0.02$) and time ($P < 0.001$). *C* and *D*: Relationships between the two adipose depots in the fasting (*C*) and postprandial (*D*) states. The data are percentage re-esterification of fatty acids (as in *B*) in subcutaneous abdominal (abdo.) (*x*-axis) and femoral (*y*-axis) adipose tissue. *C*: Mean basal values. *D*: Average values over the postprandial period. The correlation between depots was significant for each period (see the text for statistics).

calculated from these data (Fig. 4*C*). The flux of nonesterified [$^2H_2$]palmitate was analyzed specifically as an indication of the pathway of "direct NEFA uptake." In both depots, the flux of nonesterified [$^2H_2$]palmitate (Fig. 4*D*) changed between release in the fasting and late postprandial states (this represents spillover from VLDL-TG) and uptake in the early postprandial period (reflecting the direct NEFA uptake pathway). Handling of nonesterified [$^2H_2$]palmitate was not different between the depots. There was a correlation between fasting values (net release of esterified [$^2H_2$]palmitate representing spillover from VLDL-TG) in the two depots ($r_s = 0.66$, $P = 0.03$), although not after feeding.

Net uptake of fatty acids is a combination of TG extraction and entrapment (the complement of spillover) and is measured by the net transcapillary flux. The movement of the two fatty acid tracers ([^{13}C]- and [$^2H_2$]palmitate) was therefore examined in this way (Fig. 5). The transcapillary flux of [^{13}C]palmitate (Fig. 5*A*), representing the uptake of dietary fatty acids from chylomicron-TG, was significantly greater in subcutaneous abdominal than in femoral adipose tissue. In contrast, the net transcapillary flux of [$^2H_2$]palmitate, which represents mainly the uptake of fatty acids from VLDL-TG, with a smaller component of direct plasma NEFA uptake, was not different between the two depots (Fig. 5*B*). The ratio of [^{13}C]palmitate to [$^2H_2$]palmitate transcapillary flux was calculated as an index of this preferential relative removal of [$^2H_2$]palmitate by femoral fat and showed a site × time interaction ($P = 0.054$).

DISCUSSION

We directly compared subcutaneous abdominal and femoral adipose tissue in the fasting and fed states. There were clear similarities between the two depots: ATBF increased in response to meal ingestion, and the pathways of fat deposition were qualitatively similar between the two depots. The depots differed in one respect: whereas chylomicron-TG was clearly the favored source for postprandial fat deposition in subcutaneous abdominal fat, the femoral depot discriminated less against VLDL-TG.

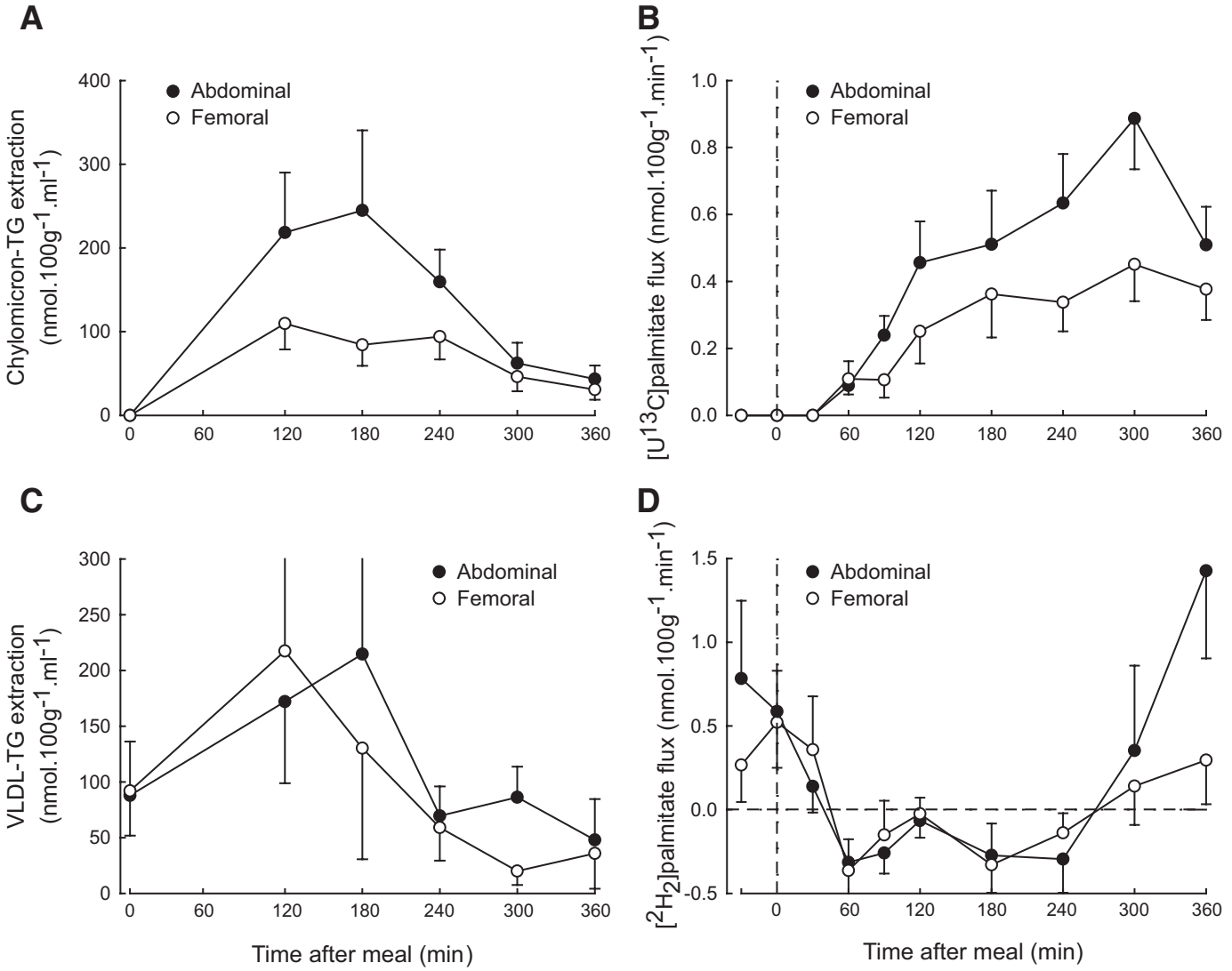


FIG. 4. Tracer-based measurements of chylomicron- and VLDL-TG extraction by the two adipose tissue depots. *A*: Extraction of chylomicron-TG. *B*: Net flux (expressed as release) of nonesterified [$U^{13}C$]palmitate from adipose tissue ("spillover"). *C*: Extraction of VLDL-TG. *D*: Net flux (expressed as release) of nonesterified [$^2H_2$]palmitate across adipose tissue (negative values therefore show net uptake). RM-ANOVA shows the following: chylomicron-TG extraction, main effects of time ($P = 0.03$) and site ($P = 0.03$); [$U^{13}C$]palmitate flux, main effects of site ($P = 0.025$) and time ($P < 0.001$); VLDL-TG extraction, no significant effects; [$^2H_2$]palmitate flux, main effect of time ($P = 0.02$) with no effect of site ($P = 0.20$) or time × site interaction.

Regulation of femoral ATBF has not been so extensively studied as has that in the abdominal depot. In postabsorptive lean subjects, subcutaneous abdominal ATBF has been reported to be higher than femoral ATBF (34,35) and gluteal ATBF (36), whereas other studies have reported that abdominal and femoral ATBF are similar in lean individuals (37,38). In obese subjects, abdominal and femoral ATBF were similar (34,38), but after 7 days of fasting, abdominal ATBF increased, whereas femoral ATBF did not (34). In the present study, we showed qualitatively similar responses in the two depots to meal ingestion. This has been shown previously after a carbohydrate-rich meal or a glucose load (37,38).

Of special interest, we and others have shown previously that the responsiveness of abdominal ATBF to meal ingestion varies markedly from person to person (20,38,39), partly depending on obesity status or insulin sensitivity. Jansson et al. (38) have shown that this responsiveness is also lost in obesity in the femoral fat depot. Here we show for the first time that the responsiveness of the two depots is correlated over a relatively normal BMI range. Although we did not assess sympathoadrenal responses in this study, the postprandial increase in ATBF is largely mediated via β-adrenergic receptors (37,40), and it may be that the sympathoadrenal response to meal intake varies between individuals and is one reason for this similarity in the two depots.

Ours is not the first study to examine lower-body adipose depots by measurements of arterio-venous differences. Indeed, one of the earliest studies of NEFA metabolism used saphenous vein measurements to demonstrate NEFA release from subcutaneous adipose tissue and showed that it was suppressed after glucose and insulin administration (41). More recently, Tan et al. (36) cannulated veins draining gluteal fat and showed that the gluteal adipose depot is distinctly less metabolically active than the abdominal depot in the fasting state. However, the gluteal depot may have specific properties. In a series of studies by Jensen and colleagues, lower-body fat metabolism has been studied by sampling from the femoral vein,

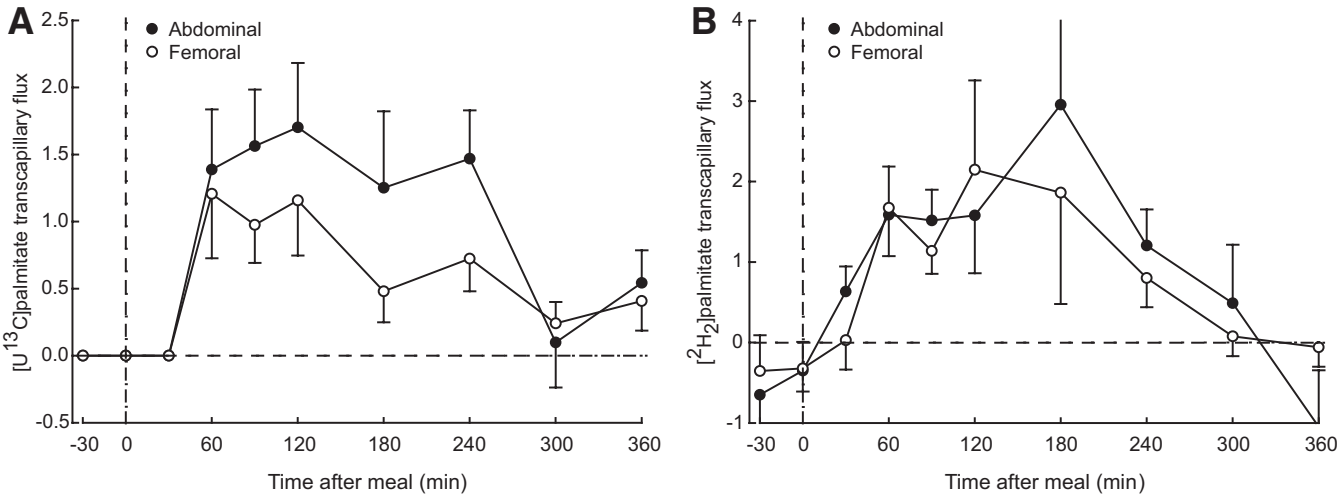


FIG. 5. Net transcapillary flux of labeled palmitic acid in the fasting and postprandial states. Units are nmol · 100 g^{-1} · min^{-1}. *A*: Net transcapillary flux of [U^{13}C]palmitate, i.e., net uptake or release of chylomicron-derived palmitate, including uptake via the LPL pathway and spillover as shown in Fig. 4*B*. *B*: Net transcapillary flux of [$^2H_2$]palmitate, i.e., net uptake or release of NEFA- and VLDL-TG–derived palmitic acid, including uptake via the LPL pathway, and direct uptake and spillover as shown in Fig. 4*D*. RM-ANOVA shows the following: net transcapillary flux of [U^{13}C]palmitate, main effects of site ($P = 0.042$) and time ($P < 0.001$); net transcapillary flux of [$^2H_2$]palmitate, main effect of time ($P = 0.012$), no effect of site ($P = 0.67$) or time × site interaction ($P = 0.13$).

which drains both adipose tissue and muscle, in conjunction with appropriate tracer measurements (rev. in 42). Upper-body subcutaneous adipose tissue shows greater rates of lipolysis than lower-body fat (when expressed as NEFA release per kilogram fat) in lean males and females in the postabsorptive state (43). After mixed-meal ingestion, leg NEFA release is more readily suppressed than upper-body subcutaneous fat in lean subjects—more so in females than males (43) and especially so in upper-body obese women (44).

We also found that femoral fat was less metabolically active than abdominal fat in many, but not all, respects. For instance, glucose uptake was similar in the two depots, which is consistent with other studies. In lean males, glucose uptake, as measured by positron emission tomography using 2-fluoro-2-deoxy-D-glucose, was similar in abdominal and femoral AT depots during normoglycemic hyperinsulinemia (45). Glucose uptake 4 h after ingestion of 100 g glucose containing a radio-tracer showed no difference between abdominal and femoral sites (46).

Some metabolic parameters were correlated between the two depots, but some were not. Particularly striking was the strong relationship between re-esterification (i.e., storage) of fatty acids in the two depots in the fed state. This did not depend on relationships with insulin concentrations, nor with sex or adiposity, and may reflect a fundamental individual characteristic of adipose tissue.

The pathway of "direct NEFA uptake" has been revealed recently from in vivo studies (29,35). Because NEFAs arise from adipose tissue, it has been suggested that this is a means of redistributing fatty acids between adipose depots (35). In our studies, direct NEFA uptake was clearly seen, and quantitatively similar, in both depots in the postprandial state, implying that there was not a net movement of fatty acids by this route from one depot to another. However, it may be that subtle differences occurring day after day can lead to significant fat redistribution, as suggested by Shadid et al. (35). A related potential mechanism for body fat redistribution, only recently studied, is the preferential delivery of VLDL-TG toward particular fat depots. VLDL-TG represents another form of recycling of adipose tissue–derived fatty acids as well as dietary fatty acids that have passed through the liver. In a recent study, women with lower-body obesity channeled a larger proportion of ex vivo–labeled VLDL-TG toward deposition in subcutaneous femoral tissue compared with abdominal adipose tissue in the postabsorptive state (47). Furthermore, the more femoral fat there is, the greater the efficiency of VLDL-TG uptake into that depot (48). This relationship between femoral fat mass and increased femoral fat uptake has also been seen in studies of meal fat deposition (49). Our data, looking for the first time at the postprandial state, suggest that the femoral depot differs from the subcutaneous abdominal in discriminating less between chylomicron- and VLDL-TG. Whereas the former was by far the major substrate for net fat uptake in the postprandial period in subcutaneous abdominal fat, this distinction was not found in the femoral depot.

In summary, we found that the femoral adipose depot was generally rather less active in terms of blood flow and fatty acid fluxes than the subcutaneous abdominal depot, when comparing responses in the fasting to feeding transition after a single meal. This is in contrast to our expectations of seeing more avid entrapment of dietary fat in the femoral depot, in keeping with its proposed role as a metabolic sink. However, it is important to distinguish short-term "transmembrane fatty acid flux" from longer-term net changes in fat mass (11). Our finding that the two depots were quantitatively similar in terms of removal of VLDL-TG and direct uptake of NEFAs suggests an interpretation that the femoral depot may act as a sink for fatty acids not immediately removed by more active depots such as the subcutaneous abdominal depot. In normal daily life in a state of energy balance, fat depots are neither expanding nor contracting. It could be that in a state of chronic positive energy balance, the femoral depot would, at least in some people, become more active in entrapment of excess dietary fat and would thus protect nonadipose tissues from ectopic fat deposition. Our studies were conducted with a single meal only. It would be important now to test this hypothesis with studies over a 24-h period (50) involving three test meals.

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S.E.M. conducted the clinical studies, collated data, and wrote the first draft of the article. S.M.H. supervised analyses, helped with calculations and statistics, and contributed to the article. L.H. made all the tracer measurements and contributed to the article. B.A.F. supervised all tracer work, helped with calculations related to tracers, and contributed to the article. F.K. was the joint project supervisor, advised on the study, and contributed to the article. K.N.F. was joint project supervisor, advised on the study, and wrote the final version of the article.

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